REMARKS

STATUS OF THE CLAIMS

Claims 34, 36, and 48-53 were pending in the application. Claims 34, and 50-53 have been amended herein. Claims 34, 36, and 48-53 will be pending if the present amendment is entered.

I. FIRST REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claims 34, 36, and 48-53 under 35 U.S.C. § 103(a), as allegedly being obvious over US Patent No. 5,837,460 ("the '460 patent") in view of Janeway et al. (Immunobiology Third Edition, 1999, pages 650-651). The Office Action alleged that the '460 patent discloses a method for ameliorating the effects of inflammation, including rheumatoid arthritis in a mammal comprising administering a therapeutically effective amount of a M-CSF antigen or antibody to a M-CSF antibody, and characterized these methods as "active immunization." The Office Action alleged it would have been obvious to substitute the claimed "passive immunization" method of treating rheumatoid arthritis with an antibody to M-CSF for the active immunization methods of the '460 patent.

Applicants respectfully maintain that claims 34, 36, and 48-53, as amended, are not obvious over '460 patent in view of Janeway et al. under 35 U.S.C. § 103(a). As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art references (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in the Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." As the Federal Circuit has also stated, "[a] general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

The Office Action stated that the '460 patent "teaches a method for ameliorating the effects of inflammation in a mammal, comprising administrating to said mammal a therapeutically effectively amount of an M-CSF or GM-CSF antigen or antibody to M-CSF or GM-CSF antibody," and cited the entire document, the Abstract, and columns 5 and 9. In fact, the '460 patent does not disclose the use of an M-CSF antigen, a GM-CSF antigen, a M-CSF antibody, or a GM-CSF antibody to treat inflammation. The Abstract of the '460 patent states that:

> A method of identifying peptides which mimic biologically active proteins is disclosed. The method comprises the steps of making a recombinant antibody library from genetic material obtained from an animal which has been immunized against antibodies that bind to the biological active protein to the mimicked. Recombinant antibodies are screened to identify antibodies which compete with the biological active protein. Peptides which comprise the recombinant antibody's CDR sequences are synthesized. Synthetic peptides which mimic GM-CSF are also disclosed.

Thus, the Abstract of the '460 patent discloses a method that involves identifying peptides from antibodies that are made against a biologically active protein. It does not relate to the use of an M-CSF antigen or M-CSF antibody to treat inflammation. In contrast, the claimed invention relates to the use of an antibody against a M-CSF, and does not relate to making an antibody against an antibody to a M-CSF.

The summary of the invention also indicates that the '460 patent relates to making synthetic peptides from antibodies against biologically active protein antibodies (col. 2, lines 20-54):

> The present invention relates to methods of identifying peptides that have 5-30 amino acids which mimic biologically active proteins. The methods of the invention comprise the steps of:
> 1) inoculating a first animal with an amount of a biologically active protein sufficient to invoke an immune response which includes antibody production by the first animal against the biologically active protein;
> 2) isolating antibodies from the first animal;
> 3) inoculating a second animal with an amount of the isolated antibodies sufficient to invoke an immune response which includes antibody production by the second animal against the anti-biologically active protein antibodies;
> 4) isolating RNA from spleen cells from the second animal and generating CDNA from such RNA;

> 5) inserting the CDNA into an expression vector to form recombinant expression vectors and introducing the recombinant expression vectors into suitable host cells to produce transformed host cells which express the CDNA and produce proteins encoded thereby;
> 6) identifying proteins which are recombinant antibodies, which bind to monoclonal antibodies specific for the biologically active protein and which compete with biological active protein to bind with monoclonal antibodies specific for the biologically active protein;
> 7) identifying amino acid sequence of complementarity determining regions of the recombinant antibodies; and
> 8) synthesizing peptides with amino acid sequence that consist of between 5-30 amino acid residues and which comprise the identified amino acid sequence.
> The present invention relates to synthetic peptides which mimic GM-CSF. (emphasis added)

The specification of the '460 patent provides additional statements about making synthetic peptides from antibodies against biologically active protein antibodies as a basis for deriving small peptides that mimic a biologically active protein on col. 5, lines 6-25:

> Essentially, antibodies are generated against the biologically active protein to be mimicked. The antibodies are then used as antigens to generate antibodies against the antibodies; some of the anti-antibodies having binding regions which mimic the biologically active protein. One an animal is confirmed to make anti-antibodies, a recombinant antibody library is generated using genetic material derived from the animal's spleen cells. The recombinant antibody library is then screened to identify a recombinant antibody which has a binding regions which mimic the biologically active protein. Such a recombinant antibody will compete with the biologically active protein such as in binding to monoclonal antibodies (MAbs) which specifically bind to the biologically active protein. Using the recombinant antibody library, one the recombinant antibody which has a binding regions which mimic the biologically active protein is identified, the amino acid sequence of the CDRs may be ascertained and that information is then used to synthesize small peptides which mimic the biologically active protein. (emphasis added).

Therefore, the Office Action is in error when it states that "US Patent '460 teaches a method for treating inflammation in a mammal using method of active immunization with M-CSF or GM-CSF antigen." It follows that the Office Action has not correctly stated the content of the art. Accordingly, a key determination of a prima facie case of

obviousness has not been made out in the Office Action. Applicants request that the rejection be withdrawn.

In addition, the '460 patent teaches away from the use of a large protein such as an M-CSF antibody to treat rheumatoid arthritis. The '460 patent states that at col. 4, lines 38 to 48:

> According to one aspect of the present invention, an efficient method is provided for identifying synthetic peptides which mimic biologically active proteins. Since peptides which mimic biologically active proteins may themselves be biologically active or inactive, the present invention is useful to find relatively small peptides which can either be administered in place of proteins or to counteract the effects of such proteins. The advantages of small peptide agonists over biologically active proteins are many. Small peptides are less immunogenic and easier and cheaper to manufacture. (emphasis added).

Therefore, the '460 patent teaches away from using a large protein such as a M-CSF antibody because the synthetic peptides of the '460 patent which are derived from an antibody to a biologically active protein antibody would be cheaper and less immunogenic according to the '460 patent. An M-CSF antibody would be expected to be more difficult and expensive to produce than a small synthetic peptide. In addition, one of skill in the art reading the '460 patent would not be motivated to use a synthetic M-CSF peptide mimic that is derived from an antibody to an M-CSF antibody to achieve active immunization because the synthetic M-CSF peptide mimic would be expected to be less immunogenic according to the '460 patent according the statement at col. 4, lines 47-48. Therefore, one of skill in the art would read the '460 patent as teaching the use of small synthetic peptides that are derived from an antibody that binds to an antibody that binds to a biologically active protein, and teaching away from the use of an antibody to a biologically active protein to treat a disease such a rheumatoid arthritis. It follows that there is insufficient motivation provided in the '460 patent to modify a synthetic peptide derived from an antibody to an antibody against a biologically active protein arrive at the claimed invention.

Moreover, Janeway et al. do not disclose how to modify a synthetic peptide derived from an antibody to an antibody to a M-CSF to arrive at a M-CSF antibody.

Janeway et al. disclose general immunization techniques. Janeway et al. however do not disclose any M-CSF sequences. Nor do Janeway et al. disclose how to modify a synthetic peptide derived from an antibody to an antibody against a biologically active protein from the '460 patent to arrive at M-CSF. Therefore, there Janeway et al. does not cure the insufficient motivation of the '460 patent to modify the cited references to arrive at the claimed invention. Also, neither Janeway et al. nor the '460 patent disclose how injecting a subject with a synthetic peptide derived from an antibody to an antibody to a M-CSF would generate antibodies against M-CSF. Thus, there also can not be a reasonable expectation of success that the combination of cited references would arrive at the claimed invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

II. SECOND REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner rejected claims 34, 36, and 48-53 under 35 U.S.C. § 103(a) as allegedly being obvious over Lopez et al. (WO 00/09561) in view of Campbell et al (1998, IDS) "as is evidence [sic] from Campbell et al. (2000, IDS)." The Office Action states that although Campbell et al. (1998, IDS) did not explicitly mention M-CSF, that it referenced the general knowledge of one skill in the art by providing a citation to Metcalf et al. (1991) and Hamilton et al. (1980). The Office Action further alleges that Campbell et al. (2000, IDS) reference the general knowledge in the art by stating that Metcalf et al. (1991) and Hamilton et al. (1980) disclose that Colony-Stimulating Factors are a family of growth factors that include M-CSF and GM-CSF. The Office Action alleged that it would have been obvious to apply the disclosure of Campbell et al. (1998) to that of Lopez et al., which allegedly discloses the use of GM-CSF antibodies to treat rheumatoid arthritis to obtain the presently claimed invention.

Applicants assert that the claims are not obvious in view of Lopez et al. in view of Campbell et al. (1998) as further evidenced by Campbell et al. (2000), or additionally in view of Metcalf et al. (1991) and Hamilton et al. (1980). As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references

or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art references (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in the Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." As the Federal Circuit has also stated, "[a] general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

GM-CSF and M-CSF have different stimulatory effects to the degree that they stimulate bone marrow precursor cells to form macrophages and granulocytes. M-CSF "tends to produce progeny committed exclusively to the formation of macrophages" (see Supplemental IDS, Metcalf (1989), Nature 339, 27-30, page 29, right hand column first lines 2-3). On page 148, last full paragraph, Metcalf et al. (1991) Phil. Trans. R. Soc. Lond. B, 333, 147-173, further states that human urinary CSF was named as M-CSF "because of its predisposition to stimulate macrophage colony formation." However, GM-CSF differs from M-CSF, because GM-CSF is "able to stimulate both granulocytic and macrophage colony stimulation." (see Metcalf (1991), at page 149, first split paragraph).

The antibodies of Lopez et al. do not bind to GM-CSF. Rather, the antibodies of Lopez et al. bind to the receptor βc that is in common with GM-CSF, IL-3, and IL-5 (see e.g., Abstract of Lopez et al.). Thus, the antibodies of Lopez et al. would be expected to block the effects of GM-CSF, IL-3, and IL-5. Thus, such antibodies would be expected to also block the effects of GM-CSF on macrophages and on granulocytes, the effects of IL-5 on B cells, and the effects of IL-3 on its target cell populations. However, as one of skill in the art would expect the M-CSF antibodies of the present invention to have their predominant effect in blocking action of M-CSF on macrophages. Unlike the antibodies of Lopez et al., that inhibit the effects of GM-CSF, IL-3, and IL-5, the M-CSF antibodies of the present invention would not be expected to have its predominant effects on inhibiting granulocytes and B cells. Also, the M-CSF antibodies of the present invention block the effects of one cytokine, M-CSF, whereas the Lopez et al. antibodies would block the effects of three cytokines - GM-CSF, IL-5, and IL-3 - by binding to the

common receptor βc. It follows that one of skill in the art would not be motivated to use an antibody to M-CSF to treat rheumatoid arthritis as it would not have those advantages of the βc receptor antibodies of Lopez et al. The Office Action has also not set out how one of skill in the art would be motivated to substitute a M-CSF antibody which binds to one cytokine in place of a βc receptor antibody that blocks the actions of three cytokines, GM-CSF, IL-3, and IL-5.

Finally, the Office Action has not disclosed how one of skill in the art would be directed to modify the βc receptor antibodies of Lopez et al. to arrive at the claimed M-CSF antibodies. The Office action lacks the element of providing a sufficient motivation to combine the cited references to arrive at the claimed invention. Thus, the Office Action does not provide a sufficient prima facie case of obviousness. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 34, 36, and 48-53 under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter for the recitation of "wherein said antibody inhibits the synergistic effects of M-CSF on MCP-1 mediated monocyte shape change."

Applicants have amended claims 34 and 50-53 to clarify the invention by deleting the phrase "wherein said antibody inhibits the synergistic effects of M-CSF on MCP-1 mediated monocyte shape change." Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112 be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance is respectfully requested.

If the Examiner believes that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at 734-622-2095.

Respectfully submitted,

Dated: March 21, 2006

Eric J. Baude
Registration No. 47,413
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105
Telephone: (734) 622-2095
Facsimile: (734) 622-1553